REMARKS

The Invention

The present invention is directed to compositions capable of inducing an immune response to cytotoxic T cell epitopes of a full length viral protein in a mammal. The composition comprises an amount of *Bacillus anthracis* anthrax PA ("PA") and a full length viral protein bound to an APABP ("APABP") sufficient to elicit a cytotoxic T lymphocyte ("CTL") immune response specific for the viral protein. The APABP comprises at least the first 250 amino acid residues of the lethal factor of *Bacillus anthracis* and less than all of the amino acid residues of the lethal factor. In some embodiments, the molar ratio of PA to the full length viral protein bound to the APABP is greater than one.

Status of the Claims

After entry of this amendment, claims 1-6 and 29-31 are pending in the application. Claim 1 has been amended to recite "viral protein." This amendment is supported in the specification at, *e.g.*, page 1, lines 16-20 and page 2, lines 1-3. New claims 29-31 have been added. The new claims find support in the specification at page 9, lines 25-31 and page 20, lines 29-31. Thus, no new matter is added by these amendments.

Claims 1-6 stand rejected under 35 U.S.C. § 103(a). This rejection is addressed in detail below.

Rejection under 35 U.S.C. § 103

Claims 1-6 stand rejected as unpatentable over Leppla *et al.*, WO 94/18332 ("Leppla *et al.*"). In making the rejection, the Examiner acknowledges that Leppla *et al.* do not teach a molar ratio of PA to full length protein bound to APABP of greater than one, but alleges that in view of the teachings of Leppla *et al.*, it would have been obvious to optimize the composition to obtain such a molar ratio. The rejection further alleges that the intended use of the claimed compositions carries no patentable weight because the claimed product is the same

as an optimized product of Leppla *et al.* Finally, the rejection alleges that Leppla *et al.* discloses the functional dosage recited in the claims. Applicants respectfully traverse each of the aspects of this rejection.

As previously explained, to establish a *prima facie* case of obviousness: (1) there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure (*see*, MPEP, § 2143, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). It is important to not that the proposed modification cannot render the prior art unsatisfactory for its intended purposes (*see*, MPEP §2143.01, citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

It is also important to note that all of the claim limitations must be considered and given weight when evaluating claims for obviousness (*see, e.g.*, MPEP § 2143.03). Moreover, as set forth in MPEP § 2173.05(g), a functional limitation in a claim must be evaluated and considered just like any other limitation.

The present invention is directed to compositions capable of inducing an immune response to cytotoxic T cell epitopes of a full length ***viral*** protein in a mammal. As amended the claims require that the compositions comprise *Bacillus anthracis* anthrax PA and full length viral protein bound to an APABP in an amount sufficient to elicit a cytotoxic T lymphocyte response. Thus, in addition to requiring a full length viral protein, the claims recite a functional element, *i.e.*, "an amount sufficient to elicit a cytotoxic T lymphocyte response specific for the viral protein," which ***is*** relevant to the patentability of the presently claimed compositions and must be given weight when evaluating the claims for obviousness under 35 U.S.C. § 103. This element is not merely an "intended use."

As discussed in detail below, neither of the required elements of the present claims are disclosed or suggested by Leppla *et al.* Moreover, one of skill in the art would have

no motivation to modify the disclosure of Leppla *et al.* to generate the presently claimed compositions Even if one of skill in the art were to modify the disclosure of Leppla *et al.*, there would be no reasonable expectation of success in generating the presently claimed vaccine compositions.

Leppla *et al.* generically discloses compositions comprising *B. anthracis* anthrax PA and peptides or proteins bound to an APABP and methods of using the compositions to deliver an activity to a cell (*e.g.*, a toxic activity). The present invention represents a separately patentable subgenus of the compositions described in Leppla *et al.* In contrast to Leppla *et al.*, the presently claimed invention is a vaccine composition using a bacterial toxin. This composition introduces a full length ***viral*** protein into the cytosol of a target cell for processing via the MHC class I pathway and presentation of viral protein epitopes by MHC class I molecules on the target cell to cytotoxic T lymphocytes to generate a cellular immune response specific for the viral protein (*see*, specification at, *e.g.*, page 3, lines 4-11 and page 18, lines 20-28).

Leppla *et al.* discloses delivery of an activity (*e.g.*, a toxic activity) to a target cell by administration of peptides or proteins bound to an APABP, but does not disclose or suggest delivery of a full length viral protein bound to an APABP to a target cell. For example, Leppla *et al.* describes the use of fusion proteins comprising toxins bound to APABP to deliver the toxin to a target cell, thus killing the target cell. In particular, Leppla *et al.* discloses method of killing HIV-1 infected cells by administration of (1) a first fusion protein comprising a ligand domain (*e.g.*, CD4) bound to the translocation and LF binding domain of PA; and (2) a second fusion protein comprising a ***toxin*** bound to APABP (*see*, Leppla *et al.* at page 6, lines 14-25, page 6, line 35 to page 7, line 7 and page 26, line 31 to page 27, line 6). The CD4 portion of the first fusion protein binds to the viral protein gp120 on the surface of the HIV-1 infected cell; the APABP portion of the second fusion protein interacts with the PA portion of the first fusion protein; and the toxin portion of the second fusion protein is internalized into the HIV-infected cell, thus killing the cell. Thus, in contrast to the presently claimed invention, Leppla *et al.* does ***not*** disclose or suggest delivery of full length viral proteins to elicit a cytotoxic T lymphocyte

response specific for the viral protein and at least one element of the invention is absent from Leppla *et al.*

In further contrast to the presently claimed invention, Leppla *et al.* contains no specific teaching or suggestion of the functional element that the compositions comprising *B. anthracis* anthrax PA and peptides or protein fragments bound to an APABP be "an amount sufficient to elicit a cytotoxic T lymphocyte response to the viral protein." As previously explained, the present invention is based on the surprising discovery that a bacterial toxin system can be used to introduce a full length viral protein into the cytosol of a target cell for processing and presentation of the viral protein via the MHC class I pathway to generate a cytotoxic T lymphocyte response (*i.e.*, a cellular immune response) specific for the viral protein. For example, the specification at page 27, lines 12-24 describes experiments demonstrating that compositions comprising a full length ***viral*** protein (*i.e.*, gp120 from HIV) bound to an APABP and translocated into an antigen-presenting cell by PA elicit a gp120-specific cytotoxic T lymphocyte response *in vivo* (*see*, page 27, lines 12-25). The processing of *B. anthracis* PA and full length viral protein (*i.e.*, gp120) bound to an APABP via the MHC class I pathway was confirmed by the use of the specific proteasome inhibitor, lactacystin which significantly decreased the gp120-specific cytotoxic T lymphocyte response to target cells contacted with the *B. anthracis* anthrax PA and full length protein bound to an APABP (*see, e.g.*, page 3, lines 4-11 and page 18, lines 20-28).

In making this rejection, the Examiner alleges that Leppla *et al.* discloses administration of a dosage (*i.e.*, 2 μg/kg to 2 mg/kg) that overlaps with the functional dosage encompassed by the present claims and concludes that Leppla *et al.* thus teaches "an amount sufficient to elicit a cytotoxic T lymphocyte response to the viral protein." The "dosage" recommended by Leppla *et al.* for administration of proteins or peptides bound to an APABP to kill a target cell is ***not*** a specific teaching of an amount of a full length viral protein bound to an APABP sufficient to elicit a cytotoxic T lymphocyte response specific for the viral protein. Leppla *et al.* does not describe any assay that could be used to determine the amount of proteins or peptides bound to an APABP sufficient to elicit a cytotoxic T lymphocyte response. Without

such guidance, one of skill in the art would not be able to identify the amount of full length viral protein bound to an APABP needed to elicit a cytotoxic T lymphocyte response specific for the viral protein. Accordingly, another element of the presently claimed invention is neither disclosed nor suggested by Leppla *et al.*

Moreover, without the teachings of the present application, one of skill in the art would have no motivation to modify the disclosure of Leppla *et al.* to make the presently claimed compositions. As previously explained, prior to the disclosure of the instant application, one of skill in the art would not have expected that an exogenously introduced full length protein could be processed and presented via the MHC class I pathway. As explained in Abbas *et al.*, CELLULAR AND MOLECULAR IMMUNOLOGY 133(Martin Wonsiewicz ed., W. B. Saunders 1991) (copy previously submitted), "endogenously synthesized antigens end up associated with class I MHC and exogenously synthesized and endocytosed antigens end up associated with class II MHC." Therefore, without impermissible hindsight, one of skill in the art would have no motivation to modify the disclosure of Leppla *et al.* to make the presently claimed compositions comprising *B. anthracis* anthrax PA and full length viral protein bound to an APABP in an amount sufficient to induce a cytotoxic T lymphocyte response (*i.e.*, a cellular immune response) specific for the viral protein.

Finally, even if one of skill in the art were to modify the disclosure of Leppla *et al.*, there would be no reasonable expectation of success in generating the presently claimed compositions. Delivery of a full length viral protein to a target cell using the presently claimed compositions would lead to processing and presentation of the viral protein by the target cell and subsequent generation of a cytotoxic T cell response specific for the viral protein, but would not kill the target cell. Thus, modification of the compositions disclosed by Leppla *et al.* to deliver viral proteins to a target cell would render the Leppla *et al.* compositions unsuitable for their intended purpose, *i.e.*, delivery of a toxic effect to a target cell.

Thus, at least two elements of the presently claimed compositions are absent from Leppla *et al.* and there is no motivation for one of skill in the art to modify the disclosure of Leppla *et al.* to make the presently claimed compositions. As such, the present invention is a

selection invention directed to a separately patentable subgenus of compositions comprising *B. anthracis* anthrax PA and full length viral protein bound to an APABP in an amount sufficient to induce a cytotoxic T lymphocyte response specific for the viral protein.

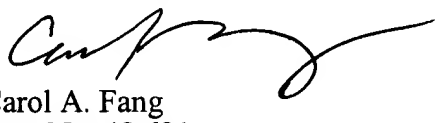
In view of the foregoing remarks, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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